REMARKS

Claims 4-12 are pending in the instant application. Claim 4 has been amended to include the nucleotide sequences of the elements in the polynucleotide cassette. No new matter has been added by virtue of this amendment and entry is respectfully requested. Any claim amendments or cancellation of subject matter is not to be construed as surrender of any subject matter. Applicants hereby reserve the right to pursue the amended or canceled subject matter in one or more continuation or divisional applications.

New claims 13 to 21 have been added. Support for these claims is found throughout the specification. For example, support for claim 13, is found in Figure 1, page 2, paragraphs [0020]-[0029]. Support for claims 14-16, is found, for example, page 2, paragraph [0037] through to page 3, paragraphs [0038]-[0043]. Support for claims 17-21, are found for example, page 3, paragraphs [0039]-[0049]. No new matter has been added by these claims and entry is respectfully requested.

Claim Rejections- 35 U.S.C. § 103

Claims 4-8, 11, and 12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Morin *et al.* (Morin *et al.*, 2000, WO 00/46355, international publication date, August 10, 2000;) in view of Li *et al.* (Li *et al.*, A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001).

Applicants respectfully traverse. However, in order to compact and expedite prosecution, Applicants have amended claim 4, to recite the nucleotide sequences of the hTERT promoter (SEQ ID NO.4), the E1A gene (SEQ ID NO.1), the IRES sequence (SEQ ID NO.3), and E1B gene (SEQ ID NO.2). New claims (claims 13 to 21) also recite these specified nucleotide sequences. These specified nucleotide sequences are not taught or disclosed by the above-described cited references. Nor are the as amended claims comprising the sequences, are predictable from the cited references, and thus the rejection should be withdrawn.

The Examiner alleges that because Li *et al.*, teaches intra-tumoral injection of the adenoviral construct, it would have been obvious to combine the teachings of Morin *et al.*, with teachings of Li *et al.* to arrive at the claimed invention (see second and third paragraphs on page 4 of Office Action). However, in contrast to the Examiner's allegations, Li teaches that there was no clear tumor reduction in the experimentation employing intra-tumoral injection (see page 6435, left column, lines 38 and 39 of Li). In fact, Li teaches only the experimental data of a single i.v. injection (i.e., systemic administration) and does not teach that of intra-tumoral injection (see e.g., Abstract of Li). Thus, Li *et al.*, teach away from an intra-tumoral injection and one of skill in the art would not perform intra-tumoral injection with any reasonable expectation of success. In contrast, the present invention caused 56.8% tumor reduction by local administration into a human patient in clinical trial (see attached draft declaration). Therefore, even if Li *et al.*, teaches an intra-tumoral injection of the adenoviral construct as the Examiner alleges, it would not have been obvious to combine the teachings of Morin *et al.* with teachings of Li *et al.* to arrive at the claimed invention, as neither teaches the claimed sequences and Li discloses that the intra-tumoral injection was ineffective.

In addition to the above, the declaration by the inventor shows the unpredictable effects of the claimed invention. Briefly, the data show that local administration of the virus (Telomelysin) to three cancer patients caused at least 20% tumor shrinkage in the cancer patients to whom it was administered without causing any serious side effects. Especially, in the patient No. 01208, local administration of Telomelysin caused 33.4% tumor shrinkage on day 28, and 56.8% tumor shrinkage on day 56 after the administration without causing any serious side effects. These results show that the virus as described in the claims is extremely effective in triggering tumor shrinkage in human subjects without causing any serious side effects. In contrast, neither of the cited references teaches or suggests that, when a recombinant virus is administered to a human subject, said administered virus will affect tumor shrinkage without triggering side effects.

In addition, the scientific journal *Science*, evaluates OBP-401 very highly, which is encompassed in the scope of the present invention, in the article of "EDITORS CHOICE" (attached

as Exhibit A; see also, *Science*, vol. 325, 11 September 2009; Kishimoto *et al., PNAS*., vol. 106, no. 34, August 25, 2009,14514-14517; attached as Exhibit B). The Editor's of the Journal, *Science*, recognized the novelty and uniqueness of the construct comprising the instantly claimed polynucleotide cassette hTERT promoter-E1A-IRES-E1B, and the vectors ability to specifically target tumor cells, opening the doorway for, *inter alia*, fluorescence -guided surgery. The value of the novel construct both scientifically and applicability to a wide-range of disciplines has thus been recognized. Morin *et al*., in view of Li *et al*., are severely deficient in such respects and the instantly claimed invention could not be predicted from the cited references.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 4, 5, 8, 9, and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Morin *et al*. (Morin *et al*., 2000, WO 00/46355, international publication date, August 10, 2000;) in view of Li *et al*. (Li *et al*., *Cancer Res*. 61(17): 6428-36, 2001) as applied to claims 4-8, 11 and 12 above, and further in view of Cheng *et al*. (Cheng *et al*., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002).

Applicants respectfully traverse. Morin *et al*., and Li *et al*., have been discussed above and for the sake of brevity will not be repeated here. Chen *et al*., do not make up for the deficiencies of Morin *et al*., in view of Li *et al*. Morin *et al*. does not teach or disclose the nucleotide sequences of the hTERT promoter (SEQ ID NO.4), the E1A gene (SEQ ID NO.1), the IRES sequence (SEQ ID NO.3), and E1B gene (SEQ ID NO.2). An intra-tumoral injection by Li *et al*., does not result in the shrinkage of a tumor and Li et al. teaches that systemic administration works best. Since Morin *et al* do not teach the construct of the invention, and Li et al. teaches away from an intra-tumoral injection, neither of these references taken together teach the instant invention. Cheng *et al*., does not teach the instant vector and provides a laundry list of possible tumors. Since the teachings of Morin *et al*., in view of Li *et al*., do not result in the instantly claimed invention, Cheng *et al*., provides nothing more than a wish list of possible tumor

treatments. Furthermore, the attached Declaration and Exhibits A and B show the uniqueness and value of the constructs as exemplified by the "Editors Choice" article. None of the references in combination or standing alone teach or disclose the instantly claimed invention.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 4-12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Morin *et al.* (Morin *et al.*, 2000, WO 00/46355, international publication date, August 10,2000) in view of Yu *et al.* (US 6,692,736, issued on 02/17/2004, filed on 03/21/2001).

Applicants respectfully traverse. Applicants have discussed Morin *et al.* above and for the sake of brevity will not be repeated here. As amended, the claims are directed to, *inter alia*, a polynucleotide cassette comprising nucleotide sequences of the hTERT promoter (SEQ ID NO.4), the E1A gene (SEQ ID NO.1), the IRES sequence (SEQ ID NO.3), and E1B gene (SEQ ID NO.2).

The Examiner alleges that Morin et al., teach a hTERT promoter to selectively direct expression and that Yu et al., "teaches a cell-specific adenovirus vector comprising target cell-specific TRE (transcriptional regulatory element) operably linked to E1A-IRES-E1B and intra-tumoral administration of the adenoviral vector, whose replication leads destruction of xenografts of cancer cells grown in a mouse...." Applicants respectfully disagree. Morin et al., do not teach the hTERT sequences of the instant invention, see, for example SEQ ID NO: 4. Furthermore, Yu *et al.*, do not teach the sequences of the instant E1A, IRES, E1B. See, for example, SEQ ID NOS: 1, 2 and 3. Therefore, combining these references do not result in the instant invention as neither teach, disclose, suggest or provide any information whereby one of skill in the art could predict the sequences taught by Applicants. Since the vectors are not taught or disclosed by the combination of these references, the methods of treating cancer are also not taught or disclosed as the vectors differ. Furthermore, the attached declaration and exhibits show the efficacy and superiority of the instantly claimed invention.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that the aforesaid claims define patentable subject matter and this application is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is being timely filed within the three month statutory period and as such no fees are believed due. Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any further extensions of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to 04-0100.

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